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Descriptive Epidemiology of Holoprosencephaly and Arhinencephaly in Metropolitan Atlanta, 1968–1992

Sonja A. Rasmussen, Cynthia A. Moore, Muin J. Khoury, and José F. Cordero

Division of Genetics, Department of Pediatrics, University of Florida College of Medicine, Gainesville, Florida (S.A.R.); Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, National Center for Environmental Health (C.A.M., M.J.K.), Office of the Director, National Immunization Program (J.F.C.), Centers for Disease Control and Prevention (C.D.C.), Atlanta, Georgia

We report the descriptive epidemiology of holoprosencephaly and arhinencephaly using data from the Metropolitan Atlanta Congenital Defects Program, a population-based birth defects surveillance system with multiple sources of ascertainment. From 1968–1992, we ascertained 63 cases of holoprosencephaly and arhinencephaly from approximately 734,000 births, for a birth prevalence of 0.86 per 10,000. Thirteen case infants with holoprosencephaly and four case infants with arhinencephaly were categorized as having syndromes. Of the case infants with non-syndromic holoprosencephaly, 55% had malformations not attributable to the underlying brain defect. The rate of holoprosencephaly and arhinencephaly increased from 0.58 per 10,000 during 1968–1972 to 1.2 per 10,000 during 1988–1992 (P for trend = 0.016). Rates were higher for females than for males (risk ratio = 1.45, 95% C.I. 0.88–2.41) and higher for nonwhites than for whites (risk ratio = 1.74, 95% C.I. 1.06–2.86). There was a U-shaped distribution of risk associated with maternal age with a slightly increased risk for younger women (risk ratio for maternal age < 20 years, compared with age 25–29 years = 1.68, 95% C.I. 0.77–3.62) and older women (risk ratio for maternal age > 34 years, compared with age 25–29 years = 2.30, 95% C.I. 0.93–5.7), but this was not statistically significant. The increased risk in the older age group could be largely explained by the presence of cases with autosomal trisomies. Neonatal mortality was higher for infants with malformations that were not attributable to the underlying brain defect and for infants with syndromes than for infants with isolated holoprosencephaly. This analysis is the first population-based study with long-term data on this rare defect. Further epidemiologic studies will be necessary to assess the risk factors for holoprosencephaly and arhinencephaly.

KEY WORDS: holoprosencephaly, arhinencephaly, epidemiology, surveillance

INTRODUCTION

Holoprosencephaly (HPE) is a developmental field defect that results from incomplete cleavage of the embryonic forebrain. This brain malformation has been classified into three types (alobar, semilobar, and lobar) [DeMyer and Zeman, 1963] and is usually accompanied by abnormalities of the face, which vary in severity from cyclopia to a single central incisor [DeMyer et al., 1964; Cohen, 1982]. The term arhinencephaly (AR) strictly refers to the absence of the olfactory tract and bulbs and may be seen as an isolated malformation or as part of the HPE spectrum. However, in the past this term has been used synonymously with HPE [Fitz, 1983; Leech and Shuman, 1986; Kobori et al., 1987]. These conditions are causally heterogeneous and have been associated with various chromosomal abnormalities [Münke et al., 1988], single-gene disorders [Cohen, 1989a], and exposure to certain teratogenic agents [Cohen, 1989b]. Recent examination of families with autosomal dominant HPE has demonstrated linkage to a gene in the 7q36 region, and evidence for genetic heterogeneity in autosomal dominant HPE has been shown [Muenke et al., 1994]. Information on the epidemiology of HPE and AR is limited [Cohen, 1989a], and available studies are based primarily on hospital or

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Address reprint requests to Dr. Cynthia Moore, Birth Defects and Genetic Diseases Branch (F45), National Center for Environmental Health, Centers for Disease Control and Prevention, 4700 Buford Highway, NE, Atlanta, GA 30341-3724.

clinic populations. We present data on the descriptive epidemiology of HPE and AR in a well-defined population over a 25-year period.

METHODS

For this study we used data from the Metropolitan Atlanta Congenital Defects Program (MACDP). This program, operated by the Centers for Disease Control and Prevention, is an ongoing birth defects surveillance registry that covers approximately 40,000 live births and stillbirths per year in the five-county metropolitan Atlanta area. Case subjects include all infants in whom serious structural defects had been diagnosed among stillbirths more than 20 weeks' gestation or weighing more than 500 g and liveborn infants in the first year of life. Cases are ascertained by hospital record review of newborns and their mothers, vital records, and cytogenetic studies. Records of hospitalized children are also periodically reviewed to ascertain other defects diagnosed in the first year of life and to modify, on the basis of results of further studies, such as genetics consultations, cytogenetic studies, radiologic examinations, and autopsies, the diagnoses for babies who had previously been ascertained as having a defect. Collection of death certificates provides mortality data on babies identified with birth defects [Edmonds et al., 1981]. Information is also recorded about significant maternal diseases, drug exposures, and family history data that are noted in hospital medical records. Each defect is coded into a six-digit code, modified from the International Classification of Diseases (ICD-9 CM) and the British Paediatric Association coding systems.

To ascertain cases of HPE and AR, we used the six-digit codes for HPE, AR, cyclopia, proboscis or tubular nose, and "other specified brain defect." We reviewed available information to confirm the presence of HPE or AR. Case infants with a severe facial defect known to be associated with HPE, including cyclopia, cebocephaly, ethmocephaly, proboscis, and single nostril, were assumed to have HPE unless brain pathologic examination or radiologic imaging demonstrated otherwise. When necessary, we reviewed the original medical records to confirm the diagnosis.

Because of concern that cases with only AR may be different from those with HPE, the analyses were done for all cases (HPE/AR) and for HPE with or without documented AR (HPE), excluding cases of AR only (AR). We analyzed the rates of this defect by sex, race, maternal age, and year of birth. The denominators used were obtained from vital records of the Maternal and Child Health Division, Georgia Department of Human Resources, for live births occurring to residents of the MACDP surveillance area for the period 1968–1992.

Cases of HPE were divided into isolated, multiple, and syndrome categories. Cases were considered isolated if they included additional minor or unspecified anomalies or anomalies that have been shown to be a part of the HPE sequence. Cases were considered multiple if the infants had at least one other unrelated major congenital anomaly but did not have a recognized genetic syndrome. Cases classified as syndromes included known single-gene conditions, chromosomal abnormalities and cases with a presumed single-gene cause that was determined on the basis of family history.

For the analyses of survival, birth weight, and small-for-gestational age (SGA) status, we evaluated cases of HPE and excluded stillbirths and pregnancy terminations. The birth weight of case infants was compared with the birth weight of infants of the same race (white vs. nonwhite) and sex who were born in Atlanta from 1982 through 1986. SGA was defined as a birth weight less than the 10th centile for gestational age, and prematurity was defined as gestational age less than 37 weeks. Chi squares, risk ratios, and 95% confidence intervals (C.I.s), and the Mantel test for trend were performed to determine statistical significance by using a statistical analysis package [James, 1990]. Statistical significance was assumed to be a P value less than 0.05.

RESULTS

We ascertained 53 cases of HPE and 10 cases of AR among the 734,272 births during the period 1968–1992. These numbers give a birth prevalence of 0.72 cases per 10,000 births for HPE and an overall birth prevalence of HPE/AR of 0.86 per 10,000. We observed an upward secular trend in the prevalence of HPE/AR (Mantel test for trend; $\chi^2 = 5.78$, $P = 0.016$) and this trend persisted when cases of AR were excluded (Table I).

Chromosome analyses were available for 37 (59%) of the case infants, and the availability of chromosome analyses increased over time. For example, during the first 12 years of the study, chromosome analysis was available for 5 of 19 (26%) case infants, but in the last 13 years (1980–1992), chromosome studies were done on 32 of 44 (73%).

We categorized 13 case infants with HPE (25%) and 4 case infants with AR (40%) as having syndromes (Table II). When syndromes were excluded, the prevalence rate of HPE/AR was 0.63 cases per 10,000 births. When we divided non-syndromic cases of HPE into isolated and multiple malformation categories, the multiple category accounted for 55% of the non-syndromic cases. Of these 22 case infants with HPE and multiple malformations, 14 (64%) had skeletal or limb malformations, 11 (50%) had cardiac malformations, 10 (45%) had malformations of the genital or reproductive system, 7 (32%) had malformations of the gastrointestinal tract, and 6 (27%) had malformations of the renal and urinary tract (see Appendix A). Nine case infants (41% of those with multiple malformations) had polydactyly.

In Table III, we show the number of cases and rates of HPE/AR by race, sex, and maternal age. Nonwhites were more likely than whites to have HPE/AR (risk ratio = 1.74; 95% C.I., 1.06–2.86). More females than males had HPE/AR (risk ratio = 1.45; 95% C.I., 0.88–2.41), and this female predominance was seen primarily in the cases with multiple malformations. However, this association was not statistically significant. These relationships were also seen among case infants with HPE, but the difference between whites and nonwhites was not statistically significant. We observed a U-shaped distribution for maternal age, with women younger than 20 years (risk ratio = 1.68; 95% C.I.,

TABLE I. Number of Cases of Holoprosencephaly and Arhinencephaly and Rates Per 10,000 Births, Metropolitan Atlanta, 1968-1992

	Holoprosencephaly and arhinencephaly HPE/AR		Holoprosencephaly HPE		
Year	Cases	Rate[a]	Cases	Rate[b]	Total births
1968–1972	8	0.58	6	0.44	137,202
1973–1977	5	0.42	5	0.42	119,136
1978–1982	11	0.83	8	0.61	132,000
1983–1987	17	1.09	15	0.96	155,966
1988–1992	22	1.16	19	1.00	189,968
Total	63	0.86	53	0.72	734,272

[a]Mantel test for trend $\chi^2 = 5.78$, $P = 0.016$.
[b]Mantel test for trend $\chi^2 = 5.89$, $P = 0.015$.

0.77–3.62), and older than 34 years (risk ratio = 2.30; 95% C.I., 0.93–5.7) being at higher risk of having an infant with HPE/AR, using the age group of 25–29 years as the referent, but this association was also not statistically significant. Of the seven case infants born to women older than 35 years of age, four had autosomal trisomies. When isolated cases were evaluated separately, this association with maternal age was not observed.

Most case infants with HPE/AR (52 of 63 cases, or 83%) were liveborn. Eight (13%) case infants were stillborn, and three cases (5%) were pregnancy terminations. Similar findings were observed for case infants with HPE with 85% being liveborn, 11% stillborn, and 4% being pregnancy terminations. Of the liveborn infants with HPE, 34 (76%) died during the neonatal period, 5 (11%) died during the first year (but after the first month), and 6 died at more than a year of age or were believed to still be alive (no death certificate located—the child was either still alive or had moved from the MACDP area) (Table IV). Infants with isolated HPE were less likely than infants with multiple malformations or syndromes to die during the neonatal period (65% for infants with isolated HPE, compared with 82% for infants with multiple malformations or syndromes), although this difference was not statistically significant. The only case with a syndrome still alive when older than 1 year of age was a child with no facial or extrafacial malformations whose sib was also affected; this child was presumed to have an autosomal recessive syndrome.

Family histories were significant for congenital malformations in nine case infants. These include two infants in our series who were born to the same parents. After HPE was diagnosed in her 7-month-old child, the mother in this family underwent a prenatal ultrasound in a subsequent pregnancy, and HPE was identified in the 22-week-old fetus. According to the medical records, neither the infant nor the fetus had any associated malformations or an identified syndrome. In addition, neither parent had any manifestations suggestive of HPE, such as single central incisor or hypotelorism, and no teratogenic exposures were noted.

Family histories were remarkable in seven other infants with non-syndromic HPE/AR. In the cases of HPE, these include a sib with a heart defect (Case 1, see Appendix A); a mother with an unspecified heart defect (Case 6); a sib with Potter's sequence (Case 14); a mother with unspecified congenital heart and renal disease (Case 13); a great uncle with multiple congenital anomalies, including an imperforate anus (Case 15); and a first cousin with spina bifida (Case 10). In one case of AR (Case 55), the mother was mentally retarded and had complete duplication of the uterus, cervix, and vagina. None of these case infants with remarkable family histories had similar defects to those in their relatives.

Regarding teratogenic exposures, mothers of four case infants with HPE (one with an inherited unbalanced

TABLE II. Syndromes Identified in Cases of Holoprosencephaly and Arhinencephaly, Metropolitan Atlanta, 1968–1992

Syndromes identified in cases with holoprosencephaly (HPE)
Chromosome abnormalities
Trisomy 13 (eight cases)
Trisomy 18 (one case)
Duplication 3p/deletion 18q (46,XY,−18,+der(18)t(3;18)(p21.1;q23)mat (one case)
Single-gene conditions
Short rib polydactyly-Saldino-Noonan (one case)
Presumed autosomal recessive (two cases—sibs)
Syndromes identified in cases with arhinencephaly only (AR)
Chromosome abnormalities
Trisomy 13 (two cases)
Trisomy 18 (one case)
Single-gene conditions
Meckel syndrome (one case)

TABLE III. Number of Cases and Rates of Holoprosencephaly and Arhinencephaly by Race, Sex, and Maternal Age, Metropolitan Atlanta, 1968–1992

Variable	Holoprosencephaly and arhinencephaly (HPE/AR)				Holoprosencephaly only (HPE)			
	No. cases	Cases/ 10,000	Risk ratio	95% C.I.	No. cases	Cases/ 10,000	Risk ratio	95% C.I.
Race								
White	31	0.67	1.00	Referent	27	0.59	1.00	Referent
Other	32	1.17	1.74	1.06–2.86[a]	26	0.95	1.63	0.95–2.79
Sex[b]								
Male	26	0.69	1.00	Referent	22	0.58	1.00	Referent
Female	36	1.01	1.45	0.88–2.41	30	0.84	1.43	0.83–2.48
Maternal age								
< 20 years	12	1.06	1.68	0.77–3.62	10	0.88	1.50	0.66–3.43
20–24 years	20	0.93	1.47	0.74–2.91	16	0.74	1.27	0.61–2.63
25–29 years	14	0.63	1.00	Referent	13	0.59	1.00	Referent
30–34 years	10	0.76	1.19	0.53–2.69	9	0.68	1.16	0.49–2.71
≥ 35 years	7	1.46	2.30	0.93–5.70	5	1.04	1.77	0.63–5.00

[a]$X^2 = 4.42, P = 0.036$.
[b]One case with sex undetermined.

chromosome translocation, the others with nonsyndromic HPE) and one case with AR had diabetes mellitus. In one case infant with HPE and Trisomy 13, evidence of cytomegalovirus (CMV) and herpes simplex virus were noted at birth, and in one infant with nonsyndromic HPE, evidence for in utero CMV infection was noted. An infant with Trisomy 18 and HPE was noted to have congenital syphilis; this infant's mother was also noted to have abused alcohol and other substances during her pregnancy. Another mother of an infant with non-syndromic HPE was noted to have consumed alcohol heavily during pregnancy. One mother of an infant with non-syndromic HPE took lithium during her pregnancy.

All of the case infants were singletons, except for one twin gestation. Both twins were girls; the case infant had short-rib polydactyly (Saldino-Noonan syndrome) and HPE and the cotwin was unaffected.

Thirteen infants with HPE/AR had been thought to have an abnormality prenatally. Most of these were recognized in recent years; before 1989 only two cases were suspected prenatally. In fact, all six case infants born in 1992 were suspected prenatally. All infants, except one, were thought to have an abnormality on the basis of prenatal ultrasonography, whereas one case infant was found to have Trisomy 13 after amniocentesis. About half of the cases (7 of 13) were recognized before 27 weeks' gestation. However, the specific brain defect was not always appreciated on prenatal evaluation. In one early case (1978), the initial diagnosis on ultrasonography was anencephaly; after pregnancy termination at 30 weeks' gestation, the final diagnosis on pathologic examination was AR, microcephaly, and occipital encephalocele. For another case infant, ventriculomegaly was noted on ultrasound at 30 weeks' gestation, but HPE was not recognized.

We analyzed cases of HPE among liveborn infants for prematurity and SGA status. Of 42 infants, 20 (48%) for whom gestational age was known were delivered at less than 37 weeks' gestation, and 26 (62%) were considered SGA. Infants with multiple malformations and syndromes were more likely to be SGA and premature than isolated cases, but this relationship was not statistically significant.

DISCUSSION

The prevalence at birth of HPE/AR in this population was 0.86 cases in 10,000 births, and the prevalence of HPE was 0.72 per 10,000 births. These results are similar to those in previous hospital-based studies in Indiana (0.63 per 10,000) [Roach et al., 1975], Spain (0.75 per 10,000) [Martínez-Frías et al., 1994], and Italy (0.769 per 10,000) [Mastroiacovo et al., 1992]. The Indiana study considered only nonchromosomal HPE; if chromosome abnormalities are excluded from our study, the prevalence of HPE/AR would be 0.68 per 10,000, and the prevalence of HPE would be 0.59 per 10,000. A higher estimate of 1.9 per 10,000 was observed in Bristol, United Kingdom, from 1979–1982 [Saunders et al., 1984], but this was based on six cases,

TABLE IV. Survival Among Liveborn Infants With Holoprosencephaly (HPE) by Type

Age at death	Isolated (%)	Multiple malformations (%)	Syndromes (%)	Total (%)
Younger than 1 month	11 (65%)	16 (84%)	7 (78%)	34 (76%)
1 month–1 year	3 (18%)	1 (5%)	1 (11%)	5 (11%)
Older than 1 year	3 (18%)	2 (11%)	1 (11%)	6 (13%)

and the rate for the same population from 1976–1979 was 0.69 per 10,000 [Saunders et al., 1984].

An upward secular trend was observed for HPE/AR in the Atlanta population. Results of the study by Saunders et al. [1984] mentioned above also suggested an increasing rate of HPE in their population. However, it is possible that our increase is due to improved ascertainment of the abnormality with the advent of better radiographic techniques. Ascertainment of early cases depended more on facial abnormalities, whereas in later years, specific information about the brain was more often available.

The risk for HPE/AR was higher among nonwhite than white infants in Atlanta. This association has not been evaluated in other epidemiologic studies of HPE. Rates of congenital malformations have been previously shown to differ among minority groups in the United States; for example, rates for microcephalus, patent ductus arteriosus, and pulmonary artery stenosis were shown to be highest among blacks, and clubfoot, hip dislocation, and hypospadias were more frequent among whites [Chávez et al., 1988]. In the Atlanta population, an increased rate of small intestinal atresia was noted among nonwhite infants [Cragan et al., 1993]. The reasons for these differences are unclear, but genetic and environmental factors and socioeconomic differences have been proposed [Chávez et al., 1988].

Previous reports have also found more females than males with HPE [Roach et al., 1975; Mastroiacovo et al., 1992]. Roach et al. [1975] reported the female predominance only among those patients with alobar HPE (at the more severe end of the spectrum). An epidemiologic study of cyclopia, representing the severe end of the holoprosencephalic spectrum, also showed a female predominance [Källén et al., 1992]. However, Mastroiacovo et al. [1992] reported the opposite relationship between severity and sex. Specific information regarding the severity of the brain defect was not available on all our cases to allow for this analysis.

One possible explanation for the female predominance is that males are more likely to be lost through spontaneous abortion. Previous studies of congenital malformations in embryos have demonstrated a much higher rate of HPE in this population [Nishimura et al., 1966; Matsunaga and Shiota, 1977], suggesting that a large proportion of embryos with this condition are lost prenatally. About half of 38 fetuses with HPE identified prenatally at 16–36 weeks' gestation were female [Berry et al., 1990], possibly suggesting an equal sex ratio earlier in pregnancy.

HPE/AR was seen more frequently among the offspring of women younger than 20 years and women 35 years and older when compared with women 25–29 years of age, although this difference was not statistically significant. The increased risk in the older age group was due to the increased frequency of nondisjunction in older mothers, with four of seven case infants born to women 35 years and older having autosomal trisomies. The relationship to increasing maternal age was also seen in the epidemiologic study of cyclopia [Källén et al., 1992]; however, their study was also plagued with a low proportion of karyotyped patients (less than 10% in their study). In Mastroiacovo's analysis [1992], the increased rate among older mothers was only observed in the chromosomal cases, but not in cases of isolated HPE or multiple malformations. A relationship between HPE and younger maternal age was not seen in the previous two studies of HPE [Källén et al., 1992; Mastroiacovo et al., 1992] but has been observed in another study of congenital malformations, with a relative risk of greater than 3 for nervous system anomalies [Croen and Shaw, 1995].

Family history in most cases of HPE/AR was unremarkable. Two case infants with HPE in our series were siblings and were presumed to have an autosomal recessive form of the condition. The remaining cases had family histories of other conditions (not structural brain defects), and no specific relationship was discernible between these conditions and HPE/AR in the case infant.

With regard to teratogenic exposures, maternal diabetes appears to be associated with a significant number of cases of HPE [Barr et al., 1983], and was noted in the five cases of HPE/AR presented here. Maternal diabetes was noted in 4 of 103 patients with cyclopia [Källén et al., 1992]. Other exposures noted in our cases that may be significant were CMV (two cases) and excessive maternal alcohol consumption (two cases); both these exposures have been associated previously with HPE [Byrne et al., 1987; Barr et al., 1983; Jellinger et al., 1981; Majewski, 1981; Pfeiffer et al., 1979; Ronen and Andrews, 1991].

In our study, a significant proportion of cases of HPE (66%) was associated with other malformations (categorized as multiples) or considered to be syndromes, similar to the results of several other studies [Berry et al., 1990; Emanuel et al., 1972; Mastroiacovo et al., 1992; Matsunaga and Shiota, 1977]. The association between chromosome abnormalities and HPE has long been recognized in the literature and was reviewed by Münke et al. [1988]. Chromosome abnormalities were observed in ten case infants with HPE and three case infants with AR. Most case infants with chromosome abnormalities had trisomy 13; there were two case infants with trisomy 18 and one infant with an unbalanced translocation involving duplication of 3p and deletion of 18q. Trisomy 13 is frequently associated with HPE, trisomy 18 has been observed in a few patients with HPE or AR, and duplication of 3p has been observed in several cases of HPE [Münke et al., 1988]. Unfortunately, chromosome analyses were not available on all our case subjects. Although we identified no infants with HPE associated with trisomy 21 as others have reported [Pi et al., 1980; Urioste et al., 1988; Epstein et al., 1988], the unavailability of cytogenetic information on all case infants does not allow us to provide any evidence of whether or not an association exists [Martínez-Frías, 1989].

We categorized four case infants as having single-gene conditions. One case infant with AR had Meckel syndrome; this condition has previously been associated with HPE/AR [Opitz and Howe, 1969; Hsia et al., 1971; Hori et al., 1980; Leech and Shuman, 1986;

Ahdab-Barmada and Claassen, 1990]. One infant with HPE had short-rib polydactyly of the Saldino-Noonan type. Although this specific relationship has not been previously recognized, short-rib polydactyly of the Majewski type has been noted in one infant [Nivelon-Chevallier, 1982]. Two of our case infants were sibs (both male), and reportedly, the parents had no signs of HPE; therefore, HPE in them was classified as probably autosomal recessive. Autosomal recessive HPE, as evidenced by affected sibships and consanguinity in some families, has been previously described [Cohen, 1989a].

It has been hypothesized that midline field defects such as HPE may be causally related to monozygotic twinning [Opitz, 1982; Suslak et al., 1987], and an increased likelihood of twinning has been observed in previous studies of HPE [Roach et al., 1975; Mastroiacovo et al., 1992] and cyclopia [Källén et al., 1992]. We are unable to support this hypothesis since all our case infants, except one (Case 48), were singletons. This case infant, with HPE and Saldino-Noonan syndrome, was most likely dizygotic, since the cotwin was unaffected with the single-gene condition, and therefore would not be relevant to this hypothesis.

Both premature and SGA cases were frequent among our series. Low birthweight was seen in 9 of 32 infants with normal karyotypes studied by Roach et al. [1975]. On the basis of our study, it appears that low birth weight observed among infants with HPE is related both to growth deficiency and prematurity.

Most case infants with HPE in MACDP died in the first month of life. This finding is similar to that in the study by Mastroiacovo et al. [1992] in which about 63% died in the first week of life. It appears that case infants with multiple malformations and syndromes are more likely to die in the neonatal period. However, six infants were believed to have survived beyond a year of life. It is possible that some of these infants died after moving from the MACDP area, and therefore were not recorded in MACDP. However, several infants with alobar HPE have been documented as surviving past a year of life [Barr and Cohen, 1992].

Several problems exist that could potentially limit the conclusions of our study. First, our prevalence rate should be viewed as an underestimate of the actual prevalence, since very mildly affected infants with HPE or AR [Hattori et al., 1987] may not be ascertained by our surveillance system. A bias toward more severe cases would modify both the survival information and epidemiologic characteristics presented here. The finding of an increased risk for HPE in females may actually be due to females being more severely affected and thus more likely ascertained in our population. In addition, ascertainment of prenatally diagnosed cases for which pregnancy termination is performed may not be complete.

Another potential problem is the broad case definition of HPE/AR. We included infants with AR in our study because the defect has been thought to represent one end of the HPE spectrum [Cohen, 1982]. In addition, this term previously (including during the early years of our study) had been used synonymously with the HPE spectrum [Fitz, 1983; Leech and Shuman, 1986; Kobori et al., 1987]. However, Cohen [1989b] has suggested that this defect may not always be part of the HPE spectrum, and although AR is frequently associated with HPE, this association is not consistent [Delezoide et al., 1990]. Therefore, in the future, AR should be considered separately from HPE in pathologic descriptions of the brain. However, because of previous confusion on this issue, we chose to include cases of AR in the epidemiologic analyses but also analyzed the cases of HPE excluding AR alone. In addition, we included infants with facial defects consistent with HPE (cyclopia, single nostril, proboscis, or tubular nose) alone in the absence of radiographic or autopsy evaluation of the brain, since we believed these infants had a high likelihood of having HPE. However, facial features of HPE have been associated with other brain defects [Akimoto et al., 1986; Lurie et al., 1992]. In a study of 82 cases of cerebral midline malformations, the facial features of cyclopia or cebocephaly always accompanied HPE [Delezoide et al., 1990], so the inadvertent inclusion of other brain defects with our broad definition, although possible, would appear to be infrequent.

Another potential problem with our study exists in the division of HPE cases into isolated, multiples and syndromes. One could argue that some cases categorized as isolated actually may more appropriately be labeled multiples. For example, infants with severe ear malformations such as anotia or microtia were included as having isolated HPE, since several infants with HPE have been shown to have this abnormality [Mastroiacovo et al., 1992; Mieden, 1982] and these malformations have been shown to be associated in epidemiologic studies [Stevens et al., 1995]. Another example is that of two infants with HPE who also had evidence of amniotic bands. This association has been seen in at least one case previously [Hunter and Carpenter, 1986], but could have been a chance occurrence; if so, these cases may be more appropriately included in the isolated category.

Further, it is likely that some infants with multiple malformations actually had chromosomal syndromes, because of the low rate of cytogenetic data in the early years of our series. We did not attempt to identify case infants with probable chromosome defects (such as trisomy 13) based on their accompanying malformations because of concern for misclassification. For example, patients with features of trisomy 13 (HPE and postaxial polydactyly) may actually have a normal karyotype as has been previously reported [Cohen, 1989a; Hennekam et al., 1991]; the term "pseudotrisomy 13" has been used to describe these infants [Cohen and Gorlin, 1991; Lurie and Wulfsberg, 1993]. However, a recent paper by Berry et al. [1990] supports our attempt to divide infants into isolated and multiple categories. None of their 17 case infants with HPE but without extrafacial malformations had cytogenetic abnormalities, whereas about half of the fetuses with extrafacial malformations had abnormal karyotypes. Therefore, this study by Berry et al. [1990] suggests that the majority of the cases in our isolated group were chromosomally normal.

Only four single-gene conditions were recognized among our case infants; however, our study is limited in this regard since parents were not routinely evaluated for mild manifestations of the condition, a process that may have resulted in identifying more patients with familial HPE. In addition, a problem may have occurred with our labelling 2 affected sibs as having a single-gene condition (presumed to be autosomal recessive). An alternative explanation is that the mother of these case infants was exposed to a teratogenic agent in both pregnancies, resulting in HPE in her two offspring.

Despite these limitations, our study represents the first population-based epidemiologic study with long-term data on HPE and AR and provides useful prevalence and epidemiologic data regarding this malformation. Continued evaluation of the Atlanta population as well as epidemiologic studies in other populations will be helpful to determine the significance of our findings.

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APPENDIX A. Summary of Holoprosencephaly Cases

			Isolated cases			
Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
1	10/06/69	F	Arhinencephaly, single cerebral hemisphere, absent pituitary gland	Anophthalmia, single central nostril	None	Unknown
2	12/25/69	M	Arhinencephaly, single cerebral hemisphere, absent pituitary gland	Tubular nose, cleft lip/palate, unilateral anotia	Small penis, talipes equinovarus	Unknown
3	05/13/70	F	Not stated	Microphthalmia, single nostril, low set ears, cleft palate, micrognathia	Flexion contractures of digits	Unknown
4	10/03/74	F	Absence of pituitary gland	Cyclopia	Absence of adrenal glands	Unknown
5	01/26/79	F	Holoprosencephaly, cerebral hypoplasia, absent corpus callosum	Cebocephaly, microphthalmia, low set ears, cleft palate	None	Normal
6	01/08/81	F	Holoprosencephaly	Microcephaly	None	Unknown
7	06/17/81	M	Holoprosencephaly	Unspecified coloboma, cleft lip	Small penis	Normal
8	03/17/82	M	Hydrocephalus	Proboscis, hypotelorism, bilateral anotia	Single umbilical artery	Normal
9	07/19/83	F	Holoprosencephaly, cortical hypoplasia, absent pituitary gland	Cebocephaly	Hypoplastic adrenal glands	Unknown
10	04/30/84	F	Holoprosencephaly	Microcephaly, hypotelorism, single nostril, cleft lip/palate, low set and posterior rotated ears	None	Normal
11	05/07/84	M	Single horseshoe-shaped cerebral mass with single ventricle, absent septum pellucidum, hydrocephaly	Cebocephaly, corneal opacity, low set ears	None	Unknown
12	09/10/84	F	Holoprosencephaly, absent corpus callosum	Microcephaly, severe midfacial hypoplasia, cleft lip/palate	None	Normal
13	07/23/85	F	Holoprosencephaly	Microcephaly, hypotelorism, midfacial hypoplasia, single nostril, cleft lip, facial palsy, lambdoidal craniosynostosis	None	Unknown
14	11/22/86	M	Holoprosencephaly, absent septum pellucidum, hypoplastic corpus callosum	Microcephaly, hypotelorism, small nares	None	Normal
15	09/03/87	M	Holoprosencephaly with single ventricle	Microcephaly, anophthalmia, cleft lip/palate, low set ears	Small penis, facial hemangioma, short neck, shield chest, umbilical hernia, posterior prominence of heels, narrow hyperconvex fingernails	Normal
16	01/30/89	M	Holoprosencephaly	Microcephaly, absent left pinna, hypoplastic right pinna	None	Normal
17	07/30/90	M	Holoprosencephaly, absence of cortex	Microcephaly, single nostril, cleft palate	Micropenis, undescended testes, bilateral foot abnormality	Normal
18	11/09/92	F	Alobar holoprosencephaly	Midline cleft lip, notched superior alveolar ridge, possible bifid uvula, possible low set ears	Short sternum, mild clinodactyly, clubbed 1st toe bilaterally, anteriorly displaced anus	Normal

(*continued*)

Cases with multiple malformations

Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
19	02/16/68	F	Fused cerebral hemispheres	Microcephaly, anophthalmia, absent nares with midline pore	Persistent truncus arteriosus, complete duplication of uterus and vagina, unspecified polydactyly, clubfeet, atresia of common bile duct	Unknown
20	02/28/69	F	Fused cerebral hemispheres, absence of posterior inferior cerebral hemispheres	Cyclopia	Duplication of left ureter	Normal
21	11/02/72	F	Single frontal lobe, hydrocephaly	Microcephaly, cebocephaly	Hypoplastic thymus, ventricular septal defect, persistent truncus arteriosus, postaxial polydactyly, webbed fingers, accessory splenic tissue in tail of pancreas, mild left hydronephrosis	Unknown
22	02/05/74	F	Holoprosencephaly with single ventricle and fused frontal lobes	Microcephaly, absence of nose, cleft lip/palate	Hypoplastic left adrenal gland, absent right adrenal gland, hemivertebrae, left clubfoot	Unknown
23	06/21/74	F	Not stated	Cyclopia, misshapen ear	Ventricular septal defect, hepatic cyst, polydactyly left hand and foot	Unknown
24	09/07/76	F	Arhinencephaly, fused frontal lobe, single anterior ventricle	Microcephaly, facial and skull asymmetry, bilateral iris colobomas, right retinal coloboma, broad nose, hypertelorism, highly-arched asymmetric palate, low set and simple ears, micrognathia, alveolar cysts with abnormal dentition	Right hydronephrosis, webbed neck, shield chest, hypoplastic labia, hypoplastic nails	Normal
25	02/06/77	M	Not stated	Microcephaly, anophthalmia, tubular nose with single opening	Imperforate anus, hypoplastic right lung	Unknown
26	04/24/79	F	Holoprosencephaly	Hypotelorism, microphthalmia, single nostril, cleft palate, low set ears	Transposition of great vessels, patent foramen ovale, enlarged lobulated kidney, bilateral postaxial polydactyly of hands	Unknown
27	01/31/80	M	Lobar holoprosencephaly, anomalous development of lateral cerebral ventricles	Not stated	Hypospadias with chordee, undescended testes	Normal
28	12/08/80	M	Monoventricular hypoplastic cerebrum, absent optic nerve	Microcephalus, anophthalmia, absent nose	Bilateral hydronephrosis, polydactyly of hands and feet, small penis, bifid scrotum	Unknown
29	06/23/84	F	Not stated	Cyclopia, proboscis, low set ears	Atrial septal defect, single ventricle, pulmonary atresia, bilaterial postaxial polydactyly of hands	Unknown

APPENDIX A. *(continued)*

Cases with multiple malformations						
Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
30	06/30/84	F	Holoprosencephaly, absent pituitary gland, absent optic nerve	Cebocephaly, anophthalmia	Pulmonary hypoplasia, bilateral hydronephrosis and hydroureter, hypoplastic ovaries and uterus, bilateral postaxial polydactyly of hands	Unknown
31	03/11/86	U	Holoprosencephaly, hydrocephalus	Microphthalmia, cataracts, low set deformed ears	Arthrogryposis at wrist, webbed neck, ambiguous genitalia, omphalocele	Unknown
32	08/07/87	M	Holoprosencephaly	Low-set ears, cleft lip/palate, defect of maxillary bone with rudimentary jaw	Left temporal scalp defect, multiple amniotic bands on hands and feet with amputation of left middle finger and right hallux, remainder of fingers fused	Normal
33	11/29/87	F	Holoprosencephaly, hydrocephaly	Microphthalmia, single nostril, malrotated low set ears	Dextrocardia with complete situs inversus, imperforate anus, ambiguous genitalia with hypoplastic vagina	Unknown
34	09/01/88	F	Holoprosencephaly	Microcephaly, cleft lip, microphthalmia, hypotelorism, proboscis, malformed ears	Atrial septal defect, bilateral polydactyly, left transverse palmar crease, thin posterior ribs, bicornate uterus, mitral valve hypoplasia, persistent truncus arteriosus, redundant neck skin	Unknown
35	01/15/89	F	Holoprosencephaly, hydrocephaly	Microcephaly	Atrial septal defect, tricuspid insufficiency, mitral insufficiency, patent ductus arteriosus, arthrogryposis multiplex congenita	Normal
36	03/15/89	F	Holoprosencephaly	Hypotelorism, cleft lip/palate, microphthalmia	Patent foramen ovale, patent ductus arteriosus, ventricular septal defect	Normal

(continued)

37	09/17/90	F	Alobar holoprosencephaly, Dandy-Walker malformation	Micrognathia, anophthalmia, low set ears	Tetralogy of Fallot, anorectal atresia, double uterus, cervicothoracic vertebral anomalies, hypoplastic adrenal glands, hypoplastic and widely-spaced nipples	Normal
38	12/29/90	F	Holoprosencephaly, hydrocephaly	Midfacial hypoplasia, hypotelorism	Patent foramen ovale, patent ductus arteriosus, accessory spleen	Normal
39	01/11/91	F	Holoprosencephaly	Cleft lip/palate, anophthalmia, absent frontal bone, absent nasal septum	Omphalocele, bilateral amniotic band amputation of fingers and toes	Normal
40	01/18/92	M	Holoprosencephaly, hydrocephaly	Anophthalmia, single nostril, low set and posteriorly rotated ears	Polydactyly of hands and feet, absent testes, micropenis	Normal

Cases with syndromes

Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
41	08/31/78	F	Holoprosencephaly	Cebocephaly	Persistent truncus arteriosus, ventricular septal defect, hydronephrosis with left ureteropelvic junction atresia, bicornuate uterus, incomplete rotation of colon	Trisomy 13
42	08/24/84	M	Holoprosencephaly	Microcephaly, cyclopia	Atrial septal defect, hypoplasia of adrenal glands, postaxial polydactyly both feet, bilateral undescended testes	3p duplication 18q deletion
43	05/16/87	M	Holoprosencephaly	Proboscis, midline cleft lip/palate	Ventricular septal defect, patent ductus arteriosus, patent foramen ovale, single coronary ostium, chordee, bilateral undescended testes, rocker bottom feet	Trisomy 13
44	08/10/87	M	Holoprosencephaly	Fused palpebral fissures, low set ears, cleft lip/palate	None	Trisomy 13
45	05/27/88	M	Holoprosencephaly	Microcephaly, low set ears, cleft lip/palate	Cutis aplasia of scalp, atrial septal defect, ventricular septal defect, small left ventricle, bilateral polydactyly of feet, absent nail on right hallux, undescended testes	Trisomy 13
46	08/20/88	M	Holoprosencephaly	Microcephaly, cyclopia	Bilateral polydactyly of hands and feet	Trisomy 13

APPENDIX A. *(continued)*

Cases with syndromes

Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
47	10/09/90	M	Lobar holoprosencephaly, absent corpus callosum	None stated	None	Normal/ presumed autosomal recessive (sib of Case 49)
48	12/18/90	F	Holoprosencephaly, absent corpus callosum, polymicrogyria, hydrocephalus, brainstem malformation	Macrocephaly, microphthalmia, cleft lip/palate, low set ears	Small chest, very short extremities, micrognathia, bilateral bifid thumbs, bilateral bifid halluces, polydactyly of right hand and left foot	Unknown/ Saldino-Noonan syndrome
49	08/21/91	M	Holoprosencephaly	Not stated	None	Normal/ presumed autosomal recessive (sib of Case 47)
50	01/23/92	M	Fused portion of cerebral ventricles	Absence right external ear and canal	Ventricular septal defect, crossed renal ectopia	Trisomy 18
51	03/30/92	F	Holoprosencephaly, absent corpus callosum, single cerebral ventricle	Bilateral cleft lip/palate, microphthalmia, bilateral cataracts	Secundum atrial septal defect, polydactyly, right transverse palmar crease, single umbilical artery, syndactyly middle fingers of left hand	Trisomy 13
52	05/15/92	F	Alobar holoprosencephaly	Single nostril, hypotelorism	Polydactyly of hands and left foot, ventricular septal defect, incomplete lobation of right lung	Trisomy 13
53	07/20/92	M	Arhinencephaly with central brain defect	Midfacial hypoplasia, partial proboscis, microphthalmia versus anophthalmia	Unspecified polydactyly, rocker bottom feet with valgus deformity, hypoplastic nails, possible transverse palmar crease right hand	Trisomy 13

APPENDIX A. *(continued)* Summary of Arhinencephaly cases

Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
54	12/07/72	F	Arhinencephaly	Microcephaly, anophthalmia	Diaphragmatic hernia, renal agenesis, absent thumbs, pulmonary hypoplasia	Normal
55	08/04/72	F	Arhinencephaly, hydrocephalus	Not stated	Omphalocele, 'spinal deformity', absence of left arm	Unknown
56	01/20/78	M	Arhinencephaly, occipital encephalocele	Microcephaly	None	Unknown

(continued)

APPENDIX A. *(continued)*

Case number	Date of birth	Sex[a]	Brain defects	Craniofacial anomalies	Other abnormalities	Karyotype/ syndrome
57	05/10/78	F	Arhinencephaly, absence of corpus callosum, hydrocephalus	Anophthalmia, low set ears, cleft palate	Meningocele, bilateral pulmonary hypolobation, patent ductus arteriosus, intestinal malrotation, cholecystic agenesis, imperforate anus, absent digit of hands and feet, transverse palmar creases, male pseudohermaphroditism	Unknown
58	08/20/78	F	Arhinencephaly	Corneal opacity, low set ears, cleft palate	Shield chest, duplication of renal arteries, hepatomegaly, dislocated elbow, hyperextended 3rd and 4th fingers, transverse palmar creases	Unknown
59	03/10/86	F	Arhinencephaly	Microcephaly, bilateral cleft lip/palate, right iris coloboma, microphthalmia	Polydactyly of feet, ventricular septal defect, atrial septal defect, bicornuate uterus, cervix and vagina, polycystic horseshoe kidney, Meckel's diverticulum	Trisomy 13
60	10/27/87	F	Arhinencephaly	Not stated	Left pulmonary artery hypoplasia, patent foramen ovale, patent ductus arteriosus, ventricular septal defect, left diaphragmatic hernia	Trisomy 18
61	05/17/88	F	Arhinencephaly, agenesis of cerebellum, polymicrogyria, occiptal encephalocele	Midline cleft palate, microphthalmia	Hypoplastic lungs, polycystic kidneys, postaxial polydactyly of hands and feet, patent foramen ovale, patent ductus arteriosus, bilateral transverse palmar creases	Unknown/ Meckel syndrome
62	07/01/88	M	Arhinencephaly, absent corpus callosum	Ethmocephaly, microphthalmia, low set ears, unspecified colobomas, hypoplastic mandible	Arthrogryposis, left talipes equinovarus, myelomeningocele, right foot with single digit and rocker bottom, syndactyly of fingers 1–4 on right and 1–2, 4–5 on left	Normal
63	08/23/90	M	Arhinencephaly	Microcephaly, bilateral cleft lip/palate microphthalmia, low set ears	Postaxial polydactyly of feet, single umbilical artery, micropenis with shawl scrotum, Meckel's diverticulum, irregular fusion of tail of pancreas to spleen, bicuspid aortic valve, patent foramen ovale, omphalocele	Trisomy 13

[a]M, male; F, female; U, undetermined.